UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,374	09/16/2003	Se-Jin Lee	JHU1800-3	5508

28213 7590 06/23/2008

DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	
MAIL DATE	**DELIVERY MODE**
06/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,374	LEE ET AL.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/29/07; 4/17/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *16 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1 and 5-15 are currently pending in the instant application.

In response to a previous Office action, a final action (mailed on May 1, 2007), applicants filed an amendment on October 29, 2007, amending claim 1 and cancelling claims 2-3 is acknowledged. Claims 4 and 16-66 remain cancelled.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 28, 2007 has been entered.

Election/Restriction

Applicant's election with traverse of peptide species of SEQ ID NO: 9 in the communication filed on April 17, 2008 is acknowledged. The traversal is on the ground(s) that there would be no burden of search for the examination of all the 15 peptide sequences simultaneously. This is not found persuasive because the instant invention represents structurally different peptides. Therefore, where structural identity is required, such as for antibody binding, the different sequences have different effects. In addition, the species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record. Furthermore, a search for each of the sequences would not be done solely by searching

electronic sequence databases as such databases seldom provide extensive coverage of all variants which are known or have been made of a single protein such that word searching for each variant is required. Furthermore, even sequence searching of the 15 different sequences would be a substantial burden on the office as each sequence has to be examined individually. Restriction is clearly permissible even among related inventions or related species as defined in MPEP 808, and 35 U.S.C. 121 allows restriction of inventions, which are independent or distinct. The examiner would like to state that this requirement is a species election, and if elected species is found allowable, the other species would be searched and if found novel would be rejoined.

The requirement is still deemed proper and is therefore made FINAL.

Applicants' arguments filed on April 17, 2008 and December 28, 2007 have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Maintained - Claim Rejections - 35 U.S.C. § 112

Previous rejection of claims 1 and 5-15 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. This rejection has been described in length in previous Office Action. The rejection is maintained for the following reasons.

These claims are directed to a method of modulating any myostatin protein activation, comprising contacting any latent myostatin complex comprising any myostatin pro-peptide and any myostatin C-terminal fragment, and a metalloprotease, wherein the metalloprotease is bone morphogenic protein-1/tolloid (BMP-1/TLD) family member that can cleave the myostatin pro-

peptide, with an agent of SEQ ID NO: 9 that increases or decreases proteolytic cleavage of the pro-peptide by said metalloprotease, thereby modulating myostatin activation.

Applicants argue that the genus of agents having inhibitory function of myostatin activation is structurally diverse as it broadly encompasses many mutants and variants comprising the functions having different structures. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 1 to limit the metalloprotease to bone morphogenic protein- 1 (BMP- 1), and the agent to a peptide selected from the group consisting of SEQ ID NO: 9-22 and 23. Applicants also argue that few representative species of myostatin is disclosed in the specification such human promyostatin (SEQ ID NOS: 1 and 2), bovine promyostatin (SEQ ID NOS: 3 and 4) chicken promyostatin (SEQ ID NO: 5 and 6), and Zebra fish promyostatin (SEQ ID NOS: 7 and 8).

Applicant's arguments and amendments to the claims have been fully considered but are not deemed to be persuasive to overcome the rejection on written description issues. The Examiner acknowledges that claims are substantially amended by adding limitation of BMP-1 and structural feature of agents but disagrees with the applicants' contention that the claims genus are fully described. Claims still read on using any BMP-1 having any structural feature and any myostatin having no structural feature used in the claimed method. Although, applicants in the remarks shows several species but claim does not correlate with applicants arguments or what is present in the specification. Besides, the species of myostatin cannot be the representative of the entire genus of myostatin and one of ordinary skill in the art cannot practice the claimed invention without knowing the specific structural feature of myostatin and BMP-1

correlated with functional feature, which is required for fulfilling written description requirement. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient structure and variety of species to reflect the representative structure variation within the genus.** Satisfactory disclosure of a representative structure and number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of species disclosed. For inventions in an unpredictable art, adequate written description of a genus cannot be achieved by disclosing the structure of small portion of only one species within the genus. The genus of myostatin or BMP-1 is structurally diverse as it broadly encompasses many mutants and variants comprising said functions having different structures. As such, the disclosure solely of functional features coupled with minor structural feature that may or may not present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus. Therefore, the rejection is maintained.

Previous rejection of claims 1 and 5-15 under 35 U.S.C. 112, first paragraph, on scope of

enablement issues is maintained. This rejection has been described in length in previous Office Action. The rejection is maintained for the following reasons.

Applicants argue that in order to expedite prosecution of the instant application, applicants have amended claim 1 to limit the metalloprotease to bone morphogenic protein-1 (BMP-1), and the agent to a peptide selected from the group consisting of SEQ ID NO: 9-22 and 23. Applicants submit that in view of the instant specification, one of skill in the art would not be faced with undue experimentation to produce and test an infinite number of possible agents to practice the invention as claimed.

Applicant's arguments and amendments to the claims have been fully considered but are not deemed to be persuasive to overcome the rejection on scope of enablement issues.

As mentioned in the previous Office Actions, claims, while being enabling for a method of modulating activation of myostatin protein of SEQ ID NO: 2 by a metalloprotease of human BMP-1 that can cleave the myostatin pro-peptide, with peptide agents such as SEQ ID NO: 9-23 that decreases proteolytic cleavage of the pro-peptide by the metalloprotease BMP-1, thereby decrease myostatin activation, doe not reasonably provide enablement for a method of modulating any myostatin protein activation, comprising contacting any latent myostatin complex comprising any myostatin pro-peptide and any myostatin C-terminal fragment, by using any BMP-1 metalloprotease that can cleave the myostatin pro-peptide, with any agent that increases or decreases proteolytic cleavage of the pro-peptide by the metalloprotease, thereby modulating myostatin activation.

Claims are so broad as to encompass a method of modulating any myostatin activation (any BMP-1 metalloprotease specific) by using agent of SEQ ID NO: 9 that increases or

decreases proteolytic cleavage of the pro-peptide, thereby modulating any myostatin activation. The scope of the claims is very broad comprising extremely large numbers of myostatin and BMP-1 proteins broadly encompassed by the claims. The claims read on any myostatin and any BMP-1 metalloprotease without any structural limitations i.e. claims do not provide any structural feature of said proteins used in the method. However, in this case the disclosure is limited to the amino acid sequences of only a few myostatin polypeptides and single BMP-1 protein.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function and physicochemical properties.

For example, Branden et al. (1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes i.e. each of the myostatin and metalloprotease proteins from different genus or species are different even within the genus or species are different and may

exhibit different functions, and physicochemical properties. However, in the instant case the disclosure is limited to the few representative species of myostatin and single re4presenattive of BMP-1 metalloprotease. The specification clearly requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of proteins have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of modulating any myostatin activation (any BMP-1 metalloprotease specific) by using the agent of SEQ ID NO: 9 that increases or decreases proteolytic cleavage of the pro-peptide, thereby modulating myostatin activation. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a peptide agent that modulates metalloprotease-mediated activation of latent myostatin having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). Therefore, the rejection is maintained.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Previous rejection of Claims 1 and 5-15 under 35 U.S.C. 102(e) as being anticipated by Lee et al. (US PGPUB 2002/0157126 A1, publication 10/24/2002, filing date 4/24/2001, claim priority of 60/054,461 of 8/1/1997, see PTO-892) is maintained. This rejection has been described at length in previous Office Action. The rejection is maintained for the following reasons.

Instant claims are directed to a method of modulating any myostatin protein activation, comprising contacting any latent myostatin complex comprising any myostatin pro-peptide and any myostatin C-terminal fragment, and a metalloprotease, wherein the metalloprotease is bone morphogenic protein-1/tolloid (BMP-1/TLD) family member that can cleave the myostatin pro-peptide, with an agent of SEQ ID NO: 9 that increases or decreases proteolytic cleavage of the pro-peptide by said metalloprotease, thereby modulating myostatin activation.

Applicants argue that to anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. Applicants' also argue that in order to expedite prosecution of the instant application, applicants have amended claim 1 to limit the metalloprotease to bone morphogenic protein-1 (BMP-1), and the agent to a peptide selected from the group consisting of SEQ ID NO: 9-22 and 23. Accordingly, Applicants submit that Lee

fails to disclose each and every element of the claimed invention, and request withdrawal of the rejection.

This is not found persuasive because Lee et al. indeed disclose a method of modulating a myostatin activation, comprising contacting a latent myostatin complex comprising a myostatin pro-peptide and a myostatin C-terminal fragment and BMP-1 that can cleave the myostatin pro-peptide into prodomain i.e. N-terminal fragment and mature myostatin i.e. C-terminal fragment, with an agent (peptides) that decreases proteolytic cleavage of the pro-peptide by the BMP-1, thereby modulating myostatin activation. Lee et al. teach a peptide/polypeptide, which is 100% identical to SEQ ID NO: 9, the agent used by the instant invention. Lee et al. indeed teach BMP-1 (see p3, Col 2, paragraph 2, line 19), a metalloprotease of BMP family. Lee et al. further teach a method of increasing myostatin activation. Lee et al. furthermore teach the method, which comprise in vitro and in vivo methods of myostatin activation. Lee et al. also teach administering the agent to a subject wherein the agent decrease proteolytic cleavage of the propeptide by the metalloprotease, thereby increase muscle mass and decrease fat content in said subject, wherein the subject an animal raised as a food source, such as avian or piscine species or ovine, porcine or bovine species or chicken or turkey or a human subject. In addition, Lee et al. teach peptide, which can be made by peptide synthesizer, as well as gene encoding pro-myostatin, BMP, a metalloprotease and how to cleave pro-myostatin and how to inhibit including assay method. In addition, Lee et al. teach administering said peptide into animal, i.e. Lee et al. teach every claimed element and how to make pro-myostatin, myostatin, assay method of cleavage, use of inhibitor or agent, which inhibit cleavage as well as how to use.

Therefore, Lee et al. anticipates claims 1 and 5-15 of the instant application and the rejection is maintained.

Conclusion

Claims 1 and 5-15 are pending.

Claims 1 and 5-15 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)?

Iqbal Chowdhury, PhD Patent Examiner
Art Unit 1652 (Recombinant Enzymes)
US Patent and Trademark Office
Remsen Bldg., Rm. 2B69, Mail Box. 2C70
Ph. (571)-272-8137, Fax. (571)-273-8137

/Iqbal H. Chowdhury/
Examiner, Art Unit 1652